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Overview: A Framework for the Discussion of Sleep in Multiple Sclerosis

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Abstract

Purpose of review—This review will focus on the causes, consequences, workup, and treatment of sleep disordered breathing, insomnia, and restless legs syndrome in patients with MS. An approach to the discussion of sleep problems and associated symptoms with MS patients, to facilitate timely and accurate diagnosis, is emphasized.

Recent findings—Recent research suggests that sleep disordered breathing, insomnia, and restless legs syndrome disproportionately affect patients with MS, and contribute to substantial morbidity in this population.

Summary—Sleep disordered breathing, insomnia, and restless legs syndrome are common but frequently under-recognized conditions in patients with MS. Additional efforts are needed to incorporate discussions about sleep into the clinical evaluation of MS patients. Neuroanatomical features, concomitant comorbidities, and medications associated with MS may partially explain the high prevalence of these disorders in MS. Prompt identification and treatment of sleep disorders may reduce fatigue, and a thorough discussion with the MS patient about their sleep will facilitate fatigue management. Research that further characterizes recently identified relationships between sleep disturbances and other chronic symptoms in MS such as pain, depression and cognitive dysfunction could identify new pathways to improve some of the most debilitating symptoms of MS.

Keywords

Multiple sclerosis; fatigue, sleepiness; obstructive sleep apnea; insomnia; restless legs syndrome

INTRODUCTION

Multiple Sclerosis is a chronic, progressive, inflammatory disease of the brain and spinal cord. This debilitating neurologic disorder affects nearly half a million Americans, and is the leading cause of non-traumatic disability among young adults. The female to male ratio is approximately 2–3:1. Depending on which region of the nervous system is affected, MS patients may experience a variety of symptoms including hemiparesis, paraparesis,

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spasticity, visual disturbances, ataxia, dysphagia, and neurogenic bowel or bladder symptoms. Patients with MS may also suffer from a number of other disabling chronic symptoms that may not necessarily be localizable to one specific lesion in the nervous system. These include fatigue, cognitive impairment, chronic pain, and mood disturbances.

Although disease modifying therapies that target immune system function may slow or prevent further disease progression, there is still no cure for MS, and no treatments have been shown to improve or reverse existing neurological damage. Consequently, an important component of MS care includes the identification of treatable or reversible comorbid conditions that can contribute to existing symptoms. Although recent research suggests that sleep disturbances are common in MS, and have the potential to contribute to chronic symptoms, sleep evaluations are not regularly incorporated into MS clinical care. The purpose of this review is to alert the clinician to common risk factors and mimickers of sleep disturbances in the MS population, with a focus on sleep disordered breathing, insomnia, and motor disorders of sleep. An increased understanding of the most common presentations of these conditions in MS - and strategies to effectively incorporate sleep evaluations into MS patient care – will facilitate timely diagnosis and treatment of these conditions.

FATIGUE IN MS

Often, a discussion about sleep in the MS patient is prompted by a discussion about fatigue. Fatigue affects at least 75% of MS patients at some point during their disease course [1, 2], and is considered by most to be the most debilitating symptom of the condition. To optimally treat this challenging symptom, a systematic diagnostic approach that fosters a thorough understanding of patients' symptomatology, timing of symptoms, *and possible underlying etiologies*, is necessary.

Although fatigue may arise directly from the neurological and immunological processes underlying MS [3–7], several treatable comorbidities, including the sleep disorders discussed below, can also contribute to this symptom. Further complicating matters, fatigue can also co-exist with sleepiness, a more commonly recognized consequence of sleep disorders in the general population, and these subjective terms may be used interchangeably by patients. Sleep disorders have the potential to contribute to both of these symptoms in MS, but discernment of the two symptoms is necessary to generate the most accurate differential diagnosis. A case-based approach the MS patient with concomitant fatigue and sleepiness can be found in *Common Pitfalls in Sleep Medicine: Case-Based Learning* (Cambridge University Press, 2014) [8].

A suggested approach to the patient who endorses fatigue is to start with an open-ended question, followed by a series of more focused questions. A suggested strategy is to start by asking the patient about his or her level of energy. Often patients will endorse terms such as “low energy,” “fatigue,” or “tiredness”; but they should be allowed to provide their own descriptions. These open-ended questions should then be followed by a request for the patient to explain what the endorsed term means to them, in their own words.

More specific queries regarding associated symptoms, including aggravating and alleviating factors, should then be employed. The following sections will describe the assessment of sleep-related symptoms as possible triggers; however, other elements may provide useful insight into the character of the symptom. If the problem is reported to be worse during sedentary, monotonous activities than during extended physical activity, or if the patient endorses a propensity to doze off during sedentary activities, excessive sleepiness is more likely than fatigue. The use of sleep or napping as a recovery mechanism for symptoms, or reports of feeling un-refreshed after an adequate night of sleep also suggest sleepiness. Though no unified definition for fatigue exists, it is most often described as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activity” [9]. If the patient’s problem is worse during sustained mental or physical activity, developing a sense of diminishing physical or mental energy over time, fatigue may be the more appropriate descriptor.

SLEEP DISORDERED BREATHING

Obstructive sleep apnea (OSA), which is characterized by repeated episodes of upper airway obstruction and hypoxia during sleep, is one of the most common sleep disorders encountered in the general population. Although OSA is estimated to affect at least 3% of Americans [10], current studies suggest that the prevalence of OSA is even higher in patients with MS, with estimates ranging from 20 to 50% [11, 12]. The biological basis for this association is still unknown. Although MS patients are susceptible to many of the same OSA risk factors as the general population, additional risk factors associated with MS that may increase the prevalence or severity of sleep disordered breathing in this population includes impairment of brainstem motor and sensory networks that control airway patency and respiratory drive [13], progressive MS subtypes/increased disability level [13], and frequent use of several medications including anti-spasmodics benzodiazepines and opiate analgesics [14].

Despite its high prevalence, OSA is still grossly under-recognized in patients with MS. A study published in 2014 in the Journal of Clinical Sleep Medicine suggested that although more than half of MS patients seen in a tertiary care center may be at elevated risk for OSA (based on a common OSA screening questionnaire known as the STOP-Bang), only 20% of these patients carried an OSA diagnosis, suggesting a high frequency of under-evaluation [11]. A similar community-based study of patients with self-identified MS showed that although up to 21% of this community sample were at risk for OSA based on the STOP-Bang, only 4% received an OSA diagnosis [12]. Collectively, these studies highlight a significant disparity in the recognition of OSA among patients with MS. In a more recent study of respiratory disorders in severely disabled wheelchair-bound MS patients, Levy and authors identified a particularly high prevalence of OSA in this sample (26/33 subjects) [15]. Although the study was not designed to assess OSA prevalence, it supports prior evidence that MS patients, and in particular, those with higher levels of disability, may be at higher risk for OSA.

Central sleep apnea (CSA) involves repeated complete or partial reduction of airflow, due to intermittent lack of respiratory effort. Although the exact prevalence of CSA in MS is still

unknown, several case studies and two recent cross-sectional studies would suggest that patients with MS, particularly those with brainstem involvement or more disabled patients, are at elevated risk for CSA. A recent study by Lin and authors identified central sleep apnea among three out of 19 MS patients who underwent home sleep apnea testing [16]. Interestingly, patients in this study had low to moderate levels of disability, raising the question of whether the proportion of patients with CSA in this study might have been higher if more patients with higher disease burden would have been included in this study. A recent case report by Nigam and authors in 2015 demonstrated a case of severe central sleep apnea with Cheyne-Stokes breathing in a patient with secondary progressive MS with known pontomedullary lesions [17].

Obstructive sleep apnea is associated with many common daily symptoms in patients with MS, making prompt identification and treatment essential. In addition to sleepiness, OSA is also known to contribute to fatigue in both non-MS and MS populations [11, 12, 18, 19]. Multiple studies have demonstrated an association between obstructive sleep apnea and fatigue in MS patients, and one cross-sectional study also suggests that treatment of obstructive sleep apnea is associated with reductions and fatigue in patients with MS and OSA [20].

Another important symptom that has gained more recognition recently in the MS community is cognitive impairment. Impairment in verbal and visual memory, executive function, processing speed, and calculation are common in MS early on in the disease, even in patients who seem otherwise relatively unaffected by the condition [21–25]. Recent research published in 2016 demonstrated significant associations between respiratory measures associated with obstructive sleep apnea and working memory, processing speed, attention, verbal learning, and response inhibition, highlighting a potential new opportunity to treat a reversible cause of cognitive impairment in MS [26]. A prospective randomized clinical trial is now under way to evaluate the effects of CPAP treatment on cognitive function in MS (NCT02544373). Obstructive sleep apnea is also associated with diminished quality of life in MS [27].

Given the potential consequences and high prevalence of sleep disordered breathing in MS, all patients should be screened for signs and symptoms associated with sleep apnea. Patients who endorse symptoms poor sleep quality, excessive daytime sleepiness, fatigue (or similar descriptor), should be queried about symptoms of snoring, gasping or choking upon awakening, non-restorative sleep, nighttime arousals, and excessive daytime hypersomnolence. Dysarthria or dysphagia (signs of brainstem dysfunction), or presence of brainstem lesions on MRI may also signal high risk for OSA or CSA, and should alert the clinician to maintain a low threshold for sleep apnea evaluation. Patients should also be asked about medications that could contribute to OSA or CSA severity [14].

The diagnosis of obstructive and central sleep apnea in MS parallels that of non-MS patients. Polysomnography (PSG) remains the gold standard. In-laboratory PSG is favored given the prevalence of central sleep apnea and other sleep disorders in this population, which may not be as sensitively detected with home sleep studies.

As in non-MS patients, treatment with positive airway pressure (PAP) is the gold standard for the treatment of OSA in patients with MS. Although rigorous demonstration of effectiveness in MS patients has yet to be published, the general health and symptomatic benefits of PAP therapy are thought to be similarly beneficial among MS patients as compared to the general population, and should be discussed with the patient. In terms of PAP equipment selection, this author suggests working with the patient to select a mask and tubing interface that is conducive to the patient's abilities. For example, the patient who reports dexterity issues or has hemiparesis on their exam may do best with a mask that does not require complex fasteners or setup. Patients should also be asked about a history of trigeminal neuralgia, which is commonly caused by demyelinating plaques in the brainstem. Such patients may benefit from masks that minimize facial contact.

Currently, no studies to evaluate the relative efficacy of alternative treatments such as oral appliances or surgery (such as uvulopalatopharyngoplasty) in MS patients with OSA have been conducted. Although no contraindications to surgery exist, the possible neuroanatomical underpinnings of sleep disordered breathing, and anticipation of changing neurological function among MS patients, generally makes surgery less attractive option [28]. In addition, careful consideration of post-surgical risks in the setting of MS are also necessary, especially for patients who are on disease modifying therapies that affect immune system function. These risks should be discussed with the patient if surgery is considered. In select cases, oral appliances, which work by repositioning the mandible in the anterior and inferior position, may also be considered, though additional studies are necessary to determine their clinical utility and feasibility in MS. These devices may also be inappropriate for trigeminal neuralgia patients who experience pain triggered by oral stimulation.

For the treatment of central sleep apnea, options should be tailored to potential secondary causes and underlying pathophysiology. Considering the fairly frequent use of anti-spasmodics, sedatives, and opioid therapy in MS, these should be considered as a possible precipitators of underlying CSA and be minimized whenever possible. Treatments in the absence of obvious secondary causes include supplemental oxygen bilevel positive airway pressure, and adaptive servo-ventilation [28].

INSOMNIA

Insomnia is characterized by difficulty initiating or maintaining sleep. Insomnia can exist as a symptom, or as a disorder - in which case symptoms of insomnia must be associated with some form of distress about poor sleep, or lead to impairments in social, academic, or vocational functioning. The International classification of Sleep Disorders Diagnostic Manual Third Edition (ICSD-3) defines insomnia as "a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite the opportunity and circumstances for sleep, and results in some form of daytime impairment" [29]. To diagnose chronic insomnia, the ICSD also requires that the reported sleep disturbance and associated daytime symptoms be present for at least 3 months, occur at least 3 times per week, and have no better explanation by another sleep disorder [29]. Impairments in daytime functioning related to the sleep disturbance may include symptoms of fatigue, impaired

concentration or memory, mood disturbances, excessive daytime sleepiness, behavioral problems, reduced motivation or energy, impaired social, family, academic, or occupational performance, proneness to errors, and concerns or dissatisfaction with sleep[29] – many symptoms that notably overlap with chronic symptoms of MS [1, 30–35].

The ICSD also delineates specific clinical and pathophysiological subtypes of insomnia, including insomnia due to a medical condition, and insomnia due to another mental disorder. Within this framework, at least 40% of patients with MS are at increased risk for insomnia [11, 12, 28]. Some of the most common symptoms experienced by MS patients - including chronic pain, symptoms of neurogenic bladder, spasticity, anxiety and depression - all have the potential to perpetuate insomnia. In a recent study of 195 MS patients which evaluated the relationship between fatigue, OSA, and other sleep disturbances, 46% met criteria for moderate to severe clinical insomnia [11] as defined by the Insomnia Severity Index - a 7-item questionnaire with 5-point Likert scale responses designed to assess the nature, severity, and impact of insomnia in adults [36]. Furthermore, 85% of patients studied endorsed at least one nocturnal symptom (pain, tingling, spasticity, feelings of restlessness, urinary urgency, anxiety, an inability to shut off the mind, or muscle twitching) to interfere with their ability to get a good night's sleep, with 54% of patients endorsing three or more of these symptoms. In this study, number of nocturnal symptoms emerged as a strong predictor of ISI score, adjusting for other important clinical confounds. Similarly, in an anonymous survey study of 2,375 community-dwelling adults with self-identified MS, 31% of those surveyed met ISI criteria for moderate to severe insomnia, while only 10% of these patients endorsed a formal diagnosis of insomnia by a physician, highlighting a large discrepancy between insomnia prevalence and recognition in this population [12].

The potential consequences of insomnia in MS are far reaching. Depression shares a bidirectional relationship with insomnia, and may be exacerbated by the condition.[37] Chronic pain may also be exacerbated by insomnia in patients with MS, and a recent study suggests that poor sleep partially mediates the relationship between pain and depression in MS patients, making this an important component to consider in the treatment of depression [38]. A recent study using functional MRI also suggests an association between insomnia and subjective (though not objective) measures of cognitive function, as well as decreased thalamic functional connectivity [39].

This author recommends that all MS patients who endorse daytime impairment, or express concerns about prolonged sleep latency, fragmented sleep, un-refreshing sleep, or early terminal awakenings be evaluated for insomnia. Given the strong association of sleep disturbances with pain and depression [40], patients who endorse these symptoms should have a detailed assessment of their sleep habits. Any of the preceding complaints should prompt a comprehensive sleep history combined with a thorough assessment of MS-specific comorbidities and nocturnal symptoms. As with non-MS patients, further inquiries should be directed toward external factors or habits that may interfere with sleep hygiene.

Treatment of insomnia in patients with MS should start with amelioration of any precipitating causes, either prior to or in tandem with first-line therapies. Multiple medications frequently used by patients with MS, including stimulants and beta-interferons,

may also contribute to insomnia and should be assessed as part of the insomnia evaluation. Queries about the timing of medications can be particularly important in this regard. For example, beta-interferons (a class of immunotherapies used to prevent exacerbations in relapsing–remitting MS) are associated with several side effects including flu-like symptoms and insomnia, but some of these symptoms may be minimized by switching from an evening to morning administration [41–43]. Modafinil, a commonly used medication for MS fatigue [44] which has a half-life of approximately 15 hours, can also interfere with sleep initiation if taken too close to bedtime.

Chronic symptoms such as spasticity, neuropathic pain, or nocturia should be reviewed and addressed. If neuropathic pain or spasticity are contributing factors, effective medications that also have sedating properties (such as tricyclic antidepressants or antispasmodics, respectively) may be reasonable first options. When evaluating MS patients for insomnia, it is also important to consider the effects of comorbid sleep disorders (see sleep disordered breathing and restless legs syndrome sections), which can contribute to insomnia symptoms [45].

If minimization of potential triggers listed above does not lead to significant improvements in insomnia, psychological and behavioral therapies should be considered. Cognitive behavioral therapy for insomnia (CBT-I) aims to target maladaptive thoughts and behaviors that can perpetuate insomnia. The benefits of CBT-I are well studied in the general population [46–49], and early research suggests that CBT-I may serve as an effective clinical intervention for MS patients with insomnia, particularly those with comorbid depression [50, 51].

For patients who are not responsive to more conservative strategies, pharmacological therapies may be necessary. Selection of an appropriate agent should be guided in part by the drug's half-life, as well as the patient's intolerances and comorbidities. Benzodiazepine receptor agonists, melatonin receptor agonists, and newer orexin receptor antagonists are all potentially useful, though none have been studied in the context of comorbid MS. Orexin receptor antagonists may also improve sleep efficiency, latency, and maintenance [52, 53]. While generally well-tolerated, potential side effects include increased daytime somnolence or sedation, vivid dreams, worsening depression, and complex nighttime behaviors. Orexin antagonists may worsen sleep paralysis, hypnagogic and hypnopompic hallucinations, and cataplexy-like symptoms, these agents are contraindicated in patients with concomitant narcolepsy.

Although the affordability and widespread availability of over-the-counter antihistamine-containing products make them a popular treatment for insomnia, it is recommended that these agents be avoided in patients with MS. Recent evidence suggests that nocturnal antihistamine use is independently associated with increased daytime fatigue in MS patients [54].

MOTOR DISORDERS OF SLEEP

Restless legs syndrome (RLS, also known as Willis-Ekbom disease) and periodic limb movement disorder (PLMD) are motor disorders of sleep [55, 56]. Both conditions have the potential to cause disrupted sleep, share a similar pathogenesis, and have an increased prevalence among persons with MS [57–59]. For the purposes of this review, PLMD will be touched upon briefly here in the context of RLS, but the majority of this section will focus on the causes, consequences, workup, and treatment of RLS in MS.

Restless legs syndrome is defined as a restlessness or uncomfortable sensation of the lower extremities that is exacerbated by rest and inactivity, has a tendency to occur in the evening or before bedtime, and is relieved with movement [28, 55, 56]. Restless legs syndrome is generally classified as idiopathic or primary if no other cause can be identified, or secondary if caused by another comorbid medical condition known to increase vulnerability, such as MS. In MS, the prevalence of RLS is estimated to be at least 3 times that of the general population [57–62].

Periodic limb movements of sleep (PLMS) consist of rhythmic, stereotyped movements of the lower extremities during sleep. Approximately 80% of patients with RLS also have PLMS [63], yet only a limited proportion of individuals with PLMS have RLS. In the absence of sleep disturbances or daytime impairment, PLMS are considered a non-specific polysomnographic finding rather than a distinct disorder. Polysomnography is required to assess for PLMS, whereas RLS is a clinical diagnosis based on a thorough history, as opposed to polysomnography. If frequent PLMS are associated with significant sleep disruption or impairments in daytime functioning, in the absence of RLS or another sleep, neurological, or medical disorder, a diagnosis of periodic limb movement disorder (PLMD) may be made [29].

Idiopathic RLS is thought to have a genetic etiology [64–66] which results in dysfunction of brain circuits that require the neurotransmitter dopamine [67]. Impaired iron metabolism is also thought to contribute to the pathogenesis of RLS [68] [69, 70]. Restless legs syndrome has also been proposed to arise from dysfunction of downstream dopaminergic pathways that project to the spinal cord [71]. Via dopaminergic transmission, these pathways are thought to be responsible for the suppression of sensory inputs and motor excitability.

The prevalence of secondary RLS is increased in certain neurologic conditions including spinal cord injury and MS [58, 59, 72], which may support the hypothesis that RLS may arise from dysfunction of descending dopaminergic pathways. In regard to MS, some of the most pivotal work in this area has come from Manconi and investigators, who have demonstrated intriguing associations between RLS and measurements of decreased myelin integrity in the cervical spinal cord, using diffusion tensor MRI [59]. Additional work from Manconi's group has also demonstrated a link between RLS and primary progressive MS, as well as increased levels of neurologic disability [28, 62].

Certain medications used in the management of persons with neurologic conditions including MS, such as antiemetics, antipsychotic dopamine antagonists, antidepressants, and antihistamines can also cause or worsen RLS. A recent study demonstrated a significantly

higher prevalence of RLS in MS patients who endorsed the use of over-the-counter agents containing H1-receptor antagonists for sleep, as compared to patients who did not use these agents [54].

To establish a diagnosis of RLS, four essential diagnostic criteria must be present: 1) a restlessness or uncomfortable sensation of the lower extremities; 2) that is exacerbated by rest and inactivity; 3) has a tendency to occur in the evening or before bedtime; and 4) is relieved with movement [56]. Many descriptors have been used to define this sensation, including creeping, crawling, itching, burning, tightening, or tingling. Other patients will describe this sensation as painful [73]. Importantly, the ICSD requires that the reported leg symptoms are not better accounted for by another medical or behavioral condition, and that the symptoms cause some form of concern, distress, sleep disturbance, or daytime impairment for the patient. This becomes particularly important when assessing the MS patient with possible RLS. For example, symptoms of cramping, clonus, spasticity, or neuropathic pain – which are all common in MS [74] – can be difficult to discern from RLS and often require detailed, direct questioning. For example, neuropathic pain may be described as more noticeable to patients at night, when they are not distracted, which may in some ways suggest a circadian predilection. In this case, endorsement of relief with movement may be a useful way to discern RLS from neuropathic pain, even if the relief is only temporary while the movement continues. Persistent pain that is not ameliorated by movement suggests neuropathic pain. Spasticity may also become more noticeable to the patient at night, and during times of fatigue which may occur later in the day. In this case, queries regarding the nature of the leg movements is also paramount. Symptoms of leg tightness relieved by *voluntary* movement suggest RLS, while *involuntary* spasms – even if a circadian component is endorsed – suggests spasticity [28].

Although there are currently no MS-specific treatment guidelines for the treatment of RLS, in this author's experience, treatment should follow standard guidelines, with additional tailoring based on the patient's history and other comorbid conditions.

Despite the lack of available evidence to support a link between RLS and low ferritin levels in MS [62], as patients may have concomitant genetic risk factors for idiopathic RLS, iron studies are still recommended, and iron supplementation should be implemented for ferritin level less than 50 ng/ml. Reduction or discontinuation of medications and substances that can cause or worsen RLS or PLMD (dopamine antagonists, lithium, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, antihistamines, tricyclic antidepressants, alcohol, tobacco, caffeine) [75–79] is advised.

If necessary, pharmacologic treatment for RLS should be individualized based on frequency and severity of symptoms. As in non-MS patients, any patient receiving therapy for RLS should be advised and monitored for adverse side effects, augmentation, and tolerance. Dopamine agonists (pramipexole, ropinirole, and rotigotine), and the alpha-2-delta ligand gabapentin enacarbil are the only FDA-approved first-line medications for moderate to severe RLS [80, 81]. Common side effects of dopaminergic agents, including nausea, hypotension, hallucinations, and dyskinesias, should be cause for consideration of alternative treatments in MS patients who suffer from concomitant autonomic dysfunction.

Augmentation -- a phenomenon that involves worsening of RLS symptoms earlier in the day with geographic spread to other body regions -- is associated with dopaminergic agents in up to 80% of patients [82].

If dopaminergic agents are inappropriate or poorly tolerated, other drug classes should be considered. Given the high prevalence of pain and other comorbid conditions in MS, alpha-2-delta-ligands are attractive alternatives. Anticonvulsants, including gabapentin, carbamazepine, and most recently pregabalin [83] have been shown to be effective treatments for RLS and may be ideal choices for patients who suffer from concomitant conditions such as neuropathic pain or seizures, for patients who experienced augmentation on dopaminergic agents.

Benzodiazepines have demonstrated a modest therapeutic effect in RLS, but are generally considered less desirable due to other side effects on sleep and daytime sleepiness [84]. Various opioid agents, including oxycodone and methadone, may be third or fourth line agents in selected cases, but the addiction potential and side effect profile associated with opioids limit their use, and they are generally not recommended in MS patients.

CONCLUSION

Sleep disordered breathing, insomnia, and restless legs syndrome are common in patients with MS. Given the potential impact of these conditions may have on health and functional outcomes in these patients, prompt recognition and treatment, which is tailored toward the individual's clinical issues and potential underlying causes, is necessary to optimize functional status and quality-of-life.

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